RESEARCH LETTER

# Clinical symptoms, imaging, and treatment of SAPHO syndrome: a single-center study of 52 cases

Hanna Przepiera-Będzak, Marek Brzosko

Department of Rheumatology, Internal Medicine and Geriatrics, Pomeranian Medical University in Szczecin, Szczecin, Poland

**Introduction** Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a very rare disease presenting as a constellation of skin and osteoarticular symptoms. The diagnostic criteria were developed by Kahn et al[1] in 1994.

Some authors suggest that SAPHO syndrome could be considered a type of spondyloarthritis (SpA) or a type of psoriatic arthritis (PsA), but others maintain that these should be considered as separate diseases.[2,3]

Skin lesions include palmoplantar pustulosis (PPP; yellow, sterile skin pustules of the hands and feet), severe acne, and acne inversa (hidradenitis suppurativa).[1-4] Anterior chest wall involvement (most often the sternoclavicular joints and attachments of the first ribs to the sternum) is the first sign of arthritis and is associated with skin redness, edema, and pain on palpation.[1-4]

In the early stages of the disease, on bone scintigraphy, approximately 85% to 95% of patients have increased tracer intake in the anterior chest wall. On routine radiographic imaging, subchondral sclerosis and new periosteal bone formation were reported, and on computed tomography, erosions, sclerotic lesions, and new bone formation.[1-4]

The cause of SAPHO syndrome is unknown, but *Propionibacterium acne* may act as a potential antigenic trigger not only in patients with acne but also in those with PPP.[5,6] The course of the disease is often chronic and self-healing.

We report on a cohort of SAPHO patients from Poland, with a focus on clinical symptoms, imaging results, and treatment.

**Patients and methods** We studied 52 patients with SAPHO syndrome and 30 healthy volunteers serving as controls. All patients were Caucasians. SAPHO syndrome was diagnosed according to the Kahn criteria.[1]

The following data were recorded: age, sex, disease duration, type of joint involvement, type of skin lesions, bone scintigraphy results, human leukocyte antigen B27 (HLA-B27) levels, presence of rheumatoid factor, comorbidities, and treatment. Pain due to the disease was assessed using a visual analogue scale. We also assessed the Bath Ankylosing Spondylitis Disease Activity Index.

In all participants, serum levels of the following cytokines were measured: interleukin (IL)-6, IL-18, IL-23, endothelin 1 (ET-1), vascular endothelial growth factor, and epidermal growth factor. Additionally, we assessed C-reactive protein levels and erythrocyte sedimentation rate. The methods of cytokine assessment were described in our previous paper.[7]

The study was approved by the local ethics committee of the Pomeranian Medical University in Szczecin, Poland. Informed consent was obtained from all participants.

**Statistical analysis** Data distributions were assessed using the Kolmogorov–Smirnov test. Data were presented as mean (SD), a number (percentage) of patients, or median (lower and upper quartiles). The *R* values of correlations were determined, and a *P* value of less than 0.05 was considered significant. The groups were compared using the *t* test, Mann–Whitney test, or Kruskal–Wallis test. The parameters were assessed by the Pearson's $\chi^2$ test and logistic regression analysis. The statistical analysis was performed using STATISTICA version 8.0 (StatSoft, Inc., Tulsa, Oklahoma, United States).

**Results** SAPHO syndrome was more common in women (TABLE 1). All patients were negative for the presence of rheumatoid factor. Of the 23 assessed patients, 4 (17.4%) were positive for HLA-B27, while of the 20 assessed patients, 2 (10%) had positive antinuclear antibody (ANA) titers

Correspondence to:
Hanna Przepiera-Będzak, MD, PhD, Klinika Reumatologii, Chorób Wewnętrznych i Geriatrii, Pomorski Uniwersytet Medyczny w Szczecinie, Samodzielny Publiczny Szpital Kliniczny Nr 1, ul. Unii Lubelskiej 1, 71-252 Szczecin, Poland,
phone: +48 91 425 33 21 ,
email: hannapb@pum.edu.pl
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**TABLE 1** Characteristics of patients with SAPHO syndrome (n = 52)

| Parameter | | Value |
|---|---|---|
| Sex, female/male, n | | 46/6 |
| Age, y, mean (SD) | | 50.0 (12.6) |
| Disease duration, y, mean (SD) | | 2.8 (2.5) |
| Presence of skin lesions, y, mean (SD) | | 4.9 (5.6) |
| ESR, mm/h, mean (SD) | | 21.4 (18.6) |
| CRP, mg/l, mean (SD) | | 7.2 (8.4) |
| VAS, mm, mean (SD) | | 46.3 (20.2) |
| BASDAI, mean (SD) | | 4.2 (2.4) |
| Increased tracer uptake on bone scintigraphy in sternoclavicular joints | | 45 (88.2) (n = 51) |
| Increased tracer uptake on bone scintigraphy in sacroiliac joints | | 7 (13.7) (n = 51) |
| Sternoclavicular joint involvement[a] | Total | 50 (96.1) |
| | Unilateral | 30 (57.7) |
| | Bilateral | 21 (40.4) |
| Shoulder joint involvement[a] | | 19 (36.5) |
| Sternum involvement[a] | | 1 (1.9) |
| Mandible involvement[a] | | 2 (3.8) |
| Knee involvement[a] | | 9 (17.3) |
| Hip involvement[a] | | 2 (3.8) |
| Wrist joint involvement[a], unilateral | | 9 (17.3) |
| Small hand joint involvement[a], unilateral | | 7 (13.5) |
| Palmoplantar pustulosis | | 46 (88.5) |
| Acne | | 3 (5.8) |
| Absence of skin lesions | | 3 (5.8) |
| Skin lesions preceding arthritis onset | | 13 (25) |
| Skin lesions and arthritis occurring simultaneously | | 33 (63.5) |
| Arthritis preceding skin lesion onset | | 3 (5.8) |
| Hypertension | | 13 (25.0) |
| Diabetes | | 5 (9.6) |
| Hypothyroidism | | 5 (9.6) |
| Ischemic heart disease | | 4 (7.8) |
| Chronic obstructive pulmonary disease | | 4 (7.8) |
| Depression | | 3 (5.8) |
| Hepatitis B virus infection | | 2 (3.8) |
| Antiphospholipid syndrome | | 1 (1.9) |
| Sjögren syndrome | | 1 (1.9) |
| Cervical cancer | | 1 (1.9) |
| Hyperthyroidism | | 1 (1.9) |
| Ulcerative colitis | | 1 (1.9) |
| Acromegaly | | 1 (1.9) |
| Syringomyelia | | 1 (1.9) |
| Glaucoma | | 1 (1.9) |
| Lung cancer | | 1 (1.9) |
| Use of NSAIDs with sulfasalazine and antibiotics | | 8 (15.4) |
| Use of NSAIDs with methotrexate and antibiotics | | 10 (19.2) |
| Use of NSAIDs with methotrexate, glucocorticoids, and antibiotics | | 2 (3.8) |

Data are presented as number (percentage) unless otherwise indicated.

a Observed on physical examination

Abbreviations: ANA, antinuclear antibody; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs; HLA-B27, human leukocyte antigen B27; RF, rheumatoid factor; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome; VAS, visual analogue scale

and 1 (5%) had positive anticardiolipin antibody titers. Data on skin lesions, including distribution and time of onset, are presented in TABLE 1. Swelling and pain of the sternoclavicular joints were the most common joint symptoms (TABLE 1). Shoulder joint pain and symmetrical or asymmetrical swelling were observed in 36.5% of patients. The most prevalent comorbidity was hypertension, followed by hypothyroidism, diabetes, and depression (TABLE 1).

In 51 patients, bone scintigraphy was performed. In 88.2% of patients, increased tracer uptake was present in the sternoclavicular joints, and in 13.7% of patients, it was present in sacroiliac joints.

All patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs alone were used in 11 patients (21.2%). In 19 patients (36.5%), sulfasalazine (1 g/d) was added, and in 22 patients (42.3%), methotrexate (15 mg/wk). In 2 patients with mandible osteomyelitis, we decided to start prednisone (15 mg/d) due to high disease activity. Additionally, in 20 patients (38.5%) with active skin lesions, we added antibiotics (doxycycline, 100 mg/d [n = 10], or azithromycin, 1000 mg/wk [n = 10]). Details on treatment regimens including antibiotics are presented in TABLE 1.

Data on the serum levels of selected cytokines in 34 patients with SAPHO syndrome and 30 controls were reported in the previous paper by Przepiera-Będzak et al.[7] SpA patients with PPP had higher mean (SD) serum ET-1 levels (1.5 [0.7] pg/ml vs 1.2 [0.5] pg/ml, $P = 0.001$) compared with those without PPP. The serum levels of IL-18 of 227.45 pg/ml or higher were associated with an increased risk of PPP (odds ratio, 3.69; 95% CI, 1.27–10.71; $P = 0.01$). There were no significant associations between serum levels of other cytokines and SAPHO syndrome.[7,8]

**Discussion** Better knowledge on SAPHO symptoms may increase the frequency of diagnosis and be useful for rheumatologists in their daily practice. We reported on the largest group of patients with SAPHO syndrome in Poland. The disease was predominant in middle-aged women, and the most prevalent skin lesion was PPP. Swelling and pain of the sternoclavicular joints were the most common joint symptoms. Other authors reported the same associations.[1-4]

In our study, 88.2% of patients had increased tracer uptake on bone scintigraphy in the sternoclavicular joints. This is consistent with data reported by other investigators.[2-4]

Interestingly, 2 of our patients with SAPHO syndrome had mandible involvement. In one of them, it was associated with the coexistence of ulcerative colitis. Mandibular sclerosing osteitis is a rare localization of bone involvement in SAPHO syndrome and was first described by Kahn et al.[9] In the available literature, we found only a few case reports of mandibular sclerosing osteitis in SAPHO syndrome, which were usually associated with a severe course of the disease.[10] In our patients, we observed severe activity of the disease, and as treatment with methotrexate and antibiotics was ineffective, we decided to add glucocorticoids.

An increased prevalence of autoimmune diseases in patients with SAPHO syndrome has been reported.[11] In our study, the most common comorbidities were hypothyroidism and diabetes, which have an autoimmune origin. Additionally, 1 patient had Sjögren syndrome, and 1 patient had antiphospholipid syndrome (positive for anticardiolipin antibody); we found a positive antinuclear antibody test in 10% of the 20 assessed patients. This could confirm the concept that autoimmunity may be involved in the pathogenesis of SAPHO syndrome.[11]

It was reported that patients with psoriasis and PsA have an increased risk of depression.[12] SAPHO syndrome is considered a type of PsA, but we did not find data about an increased risk of depression in the available literature. In our study we observed a high prevalence of depression among SAPHO patients. Some of our patients suffered from cosmetic disability due to active PPP, and skin lesions negatively affected their interpersonal contacts. This could suggest that patients with SAPHO, similarly to those with PsA, have an increased risk of depression. Effective treatment of skin lesions would have a beneficial effect on their quality of life.

In our previous study, we found that SpA patients with PPP had increased serum levels of IL-18 compared with healthy controls, and it was associated with an increased risk of PPP. This suggested that IL-18 may be involved in the pathogenesis of skin lesions in SAPHO syndrome.[7,8]

The cause of SAPHO syndrome is unknown, and there are no standard recommendations for treatment. Usually, NSAIDs are the first-line treatment. These drugs can reduce joint symptoms but have no influence on skin lesions. In our study, NSAIDs were effective only in some patients, which is consistent with data from other studies.[2,8]

As *Propionibacterium acne* is considered an important trigger of SAPHO syndrome, the use of antibiotics might be considered.[5,6] In our study, we observed that antibiotics reduced disease activity in cases with active skin lesions, and we agree with others that antibiotics are useful in the treatment of SAPHO syndrome.[5,6]

The use of disease-modifying antirheumatic drugs, particularly methotrexate and sulfasalazine, has been reported to be effective in SAPHO syndrome.[3] In our study, in some patients, treatment with sulfasalazine reduced disease activity, but we had to switch to methotrexate in others. Additionally, in patients with mandible

osteomyelitis due to active inflammation, we decided to add glucocorticoids.

In conclusion, mandible involvement is a rare manifestation of SAPHO syndrome. An increased incidence of autoimmune diseases and depression was observed. Increased serum IL-18 levels were associated with increased risk of PPP. Treatment with disease-modifying antirheumatic drugs and antibiotics was effective.

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